of these claims is attached hereto as **Exhibit A.**

No new matter has been introduced by this Amendment. Support for claim 88 as amended appears in the specification *inter alia* at page 11, lines 17-24.

Furthermore, claim 88 as amended is similar to claim 1 of co-owned granted patent U.S. 5,965,383 which contains the phrase "and having the amino acid sequence gln-ala-gln-gln or met-gln-ala-gln-gln at the N-terminus of the polypeptide."

Support for claim 89 as amended appears in the specification *inter alia* at page 47, lines 26-33.

Thus, applicants maintain that no issue of new matter exists and respectfully requests entry of this Amendment.

Applicants will now relate to the Examiner's objections in the order set forth in the November 6, 2001 Office Action.

Claim Rejections - 35 U.S.C. §112 (first paragraph)

The Examiner maintained the rejection of claims 88-96 based on the assertion that the specification, while being enabling for the fibronectin fragments disclosed in the specification, does not reasonably provide enablement for any portion of fibronectin. The Examiner alleged that the specification does not enable a person skilled in the art to which it pertains to make and use the invention commensurate in scope with the claims.

The Examiner stated that claims 88-96 are directed to an imagining agent which comprises a polypeptide labeled with an imageable marker, wherein such polypeptide has an amino acid sequence which comprises at least one-fifth of the amino acid sequence of the N-terminal FBD of naturally-occurring fibronectin, wherein the imaging agent is capable of binding to fibrin. The Examiner further noted that the specification on page 53 describes three purified polypeptides, having molecular weights of 31 kD, 20 kD, and 12 kD derived from the first 262 amino acids of the N-terminal sequence of FBD of fibronectin, but alleged that the specification does not define the one-fifth portion of the N-terminal sequence nor any correlation between th one-fifth portion of sequence with the sequences from where the 31 kD, 20 kD, and 12 kD polypeptides are derived.

The Examiner further alleged that the specification defines the 31 kD polypeptide as corresponding to an amino acid sequence present in the FBD and having the amino acid sequence 1-262 of full length FBD of human fibronectin, and that the specification indicates that FBD commences at amino acid position 1 of mature fibronectin. The Examiner stated that if FBD is commencing at amino acid position 1, it can not lead to a conclusion that the N-terminus of FBD sequence is QAQQ. The Examiner further stated that neither the specification nor the claim defines clearly the position of the one-fifth portion in relation to the amino acid sequence of the FBD of naturally occurring fibronectin.

The Examiner further alleged that it would require undue experimentation for one of ordinary skill in the art to determine all possible imaging agents derivable, having at least one-fifth of

the amino acid sequence of the N-terminal region of FBD of fibronectin since a large number of polypeptides is easily envisioned but the determination of bilogical activity of all such polypeptides, each requiring purification, refolding and labeling, is well outside the realm of routine experimental work.

The Examiner further alleged that the specification lacks guidance as to exactly what polypeptides might possess the claimed activity, and that one of ordinary skill in the art would require guidance as to what region of fibronectin is included in the phrase the "fibrin binding domain," what specific amino acids are encompassed and what is the sequence.

In response, applicants point out that claim 88 as amended hereinabove is directed to an imaging agent which comprises a polypeptide labeled with an imageable marker, such polypeptide having an amino acid sequence of the N-terminal fibrin binding domain of naturally-occurring human fibronectin, and having the amino acid sequence gln-ala-gln-gln or met-gln-ala-gln-gln at the N-terminus of the polypeptide, and wherein the polypeptide has a molecular weight less than 31 kD.

Thus, claim 88 as now amended specifically defines the characteristics of FBD polypeptide comprising the claimed imaging agent, such that one of ordinary skill in the art would be able to make and use the invention without undue experimentation. Specifically, applicants point out that the specification defines (*inter alia* on page 47, lines 10-15) the N-terminal FBD as amino acids 1-262 of the mature fibronectin molecule. One of ordinary skill in the art would understand that the expression "one-fifth of

the amino acid sequence of the N-terminal fibrin binding domain" would comprise about 52 amino acids of that sequence. The correlation between the specific one-fifth portion of the FBD and the FBD polypeptide fragment comprising the imaging agent of the invention is provided by the expression "having the amino acid sequence gln-ala-gln-gln or met-gln-ala-gln-gln at the N-terminus of the polypeptide" (i.e. amino acids 1-4 of FBD).

Thus, applicants' polypeptide must contain at least the first consecutive one-fifth of the amino acids of the N-terminal FBD i.e. at least amino acids 1-52, since that is the only one fifth portion which could be described as having the sequence QAQQ. The one fifth portion could not be any other portion of the FBD since it would then not have the sequence QAQQ.

In sum, the polypeptide comprising the claimed imaging agent corresponds to at least amino acid residues 1-52 of the FBD and encompasses the range of progressively longer polypeptides derived from the FBD, all beginning from position 1, and all of molecular weight less than 31 kD.

Furthermore, all the disclosed embodiments of applicant's FBD polypeptides i.e. the 20 kD 20 kD' and 12 kD polypeptides each comprise amino acids 1-52 of the N-terminal FBD. Hence both the specification and the claims as amended clearly define the position of the recited one fifth portion in relation to the amino acid sequence of the FBD.

The applicants further state that claim 88 as amended is unequivocal in regard to the N-terminal FBD. Hence, both the

specification and the claims as amended clearly define the position of the recited one fifth portion in relation to the amino acid sequence of the FBD.

The applicants further state that claim 88 as amended is unambiguous in the relationship between the one-fifth portion and the sequence QAQQ. As discussed above, the one-fifth portion of the N-terminal FBD comprising the FBD polypeptide comprising the subject imaging agent is the one-fifth portion corresponding to amino acids 1-52, since that is the only one-fifth portion of the FBD having the sequence QAQQ. None of the other possible one fifth portions of the FBD have the sequence QAQQ, either at the N-terminus or at any other location.

Hence, one of ordinary skill in the art would be able without undue experimentation to carry out the claimed invention which is directed to an imaging agent which comprises a polypeptide labeled with an imageable marker, such polypeptide having an amino acid sequence which comprises at least one-fifth of the amino acid sequence of the N-terminal fibrin binding domain of naturally occurring human fibronectin, and having the amino acid sequence gln-ala-gln-gln or met-gln-ala-gln-gln at the N-terminus of the polypeptide, and wherein the polypeptide has a molecular weight less than 31 kD.

M.P.E.P Section 2164.03 provides that "even in unpredictable arts, a disclosure of every operable species is not required." Since the subject application includes a disclosure of three operable examples of the claimed invention (i.e. a 20 kD polypeptide in Example 2 and the 12 kD and 12 kD' polypeptides in Example 9),

applicants maintain that they are entitled to the scope of the claims now pending as amended above.

Furthermore, applicants should not be forced to limit their claims to the specific imaging agent disclosed in the specification i.e the 12 kD, 12 kD', and 20 kD polypeptides, since they were the first to disclose a polypeptide imaging agent corresponding to a fragment of the N-terminal fibrin binding domain of fibronectin. In particular, applicants are entitled to claim a polypeptide imaging agent which comprises at least one fifth of the amino acid sequence of the N-terminal fibrin binding domain of naturally-occurring human fibronectin, and having the amino acid sequence gln-ala-gln-gln or met-gln-ala-gln-gln at the N-terminus of the polypeptide, and wherein the polypeptide has a molecular weight less than 31 kD.

Applicants respectfully direct the Examiner's attention to U.S. v. Teletronics, Inc., 8 U.S.P.Q. 2d 1217, 1222-1223 (Fed. Cir. 1988), a copy of which is attached hereto as **Exhibit B**, where it was stated:

"A patent may be enabling even though some experimentation is necessary; the amount of experimentation, however, must not be unduly extensive."

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"Since one embodiment is admittedly disclosed in the specification, along with the general manner in which its current range was ascertained, we are convinced that other permutations of the invention could be practiced by those skilled in the art without undue experimentation. *See SRI Int'l v. Matsushita Elec. Corp. of*

America, 775 F.2d 1107, 1121 (Fed. Cir. 1985) (the law does not require an applicant to describe in his specification every conceivable embodiment of the invention); *Hybritech Inc.*, 802 F.2d at 1384 (the enablement requirement may be satisfied even though some experimentation is required)."

Applicants are entitled to generic claims such as claims 88-89 and 92-96. Legal authority supporting the grant of claims of such scope is provided by In re Angstadt and Griffin, 190 U.S.P.Q. 214 at 218 a copy of which is attached hereto as **Exhibit C**.

"Appellants have apparently not disclosed every catalyst which will work. The question then, is whether in an unpredictable art, section 112 required disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with 'thousands' of examples or the disclosure of 'thousands' of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hyperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid 'literal' infringement of such claims by merely finding another analogous catalyst complex which could be used in 'forming hydroperoxides'."

Claim 88 recites an imaging agent which comprises a polypeptide

labeled with an imageable marker, such polypeptide having an amino acid sequence which comprises at least one fifth of the amino acid sequence of the N-terminal fibrin binding domain of naturally-occurring human fibronectin, and having the amino acid sequence gln-ala-gln-gln or met-gln-ala-gln-gln at the N-terminus of the polypeptide, and wherein the polypeptide has a molecular weight less than 31 kD. Applicants respectfully submit that their teachings and exemplifications enable a person of ordinary skill in the art to practice the invention of the claim as amended.

In view of the amendment of the claims and the preceding comments, the Examiner is respectfully requested to withdraw the rejection of the claims under 35 U.S.C. §112 (first paragraph).

Claim rejections - 35 U.S.C. §112 (second paragraph)

The Examiner has rejected claims 88-96 as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

The Examiner states that it is not clear from claim 88 or the specification what is the corresponding amino acid sequence which comprises at least one fifth portion of the amino acid sequence of the N-terminal region of the fibrin binding domain of fibronectin. The Examiner further states that the recitation of the sequence gln-ala-gln-gln or met-gln-ala-gln-gln renders the claim indefinite because it is not clear what is the one-fifth portion of the amino acids in relation to the recited sequences.

In response, applicants have amended claim 88 hereinabove to

clarify that the subject imaging agent comprises a polypeptide which comprises at least one-fifth of the amino acid sequence of the N-terminal fibrin binding domain of naturally-occurring human fibronectin, and having the amino acid sequence gln-ala-gln-gln or met-gln-ala-gln-gln at the N-terminus of the polypeptide, and wherein the polypeptide has a molecular weight less than 31 kD.

Claim 88 as amended thus more clearly specifies that the one-fifth portion of the N-terminal FBD comprising the subject imaging agent is the one-fifth portion corresponding to amino acids 1-52, since that is the only one-fifth portion of the FBD which could have the sequence QAQQ. No other one-fifth portion of the FBD could possibly have the sequence QAQQ.

Furthermore, the claim as amended does not imply or suggest that the sequence QAQQ is the one-fifth portion or that one-fifth of the sequence QAQQ constitutes the subject polypeptide, as alleged by the Examiner. One skilled in the art would understand from the claim as amended that the relationship between the one-fifth portion and the recited sequences is that the one-fifth portion is either of the recited sequences as its N-terminus.

The Examiner further states that claim 89 has a step of detecting but it is not clear from the claim that "detecting" would per se result in "imaging," and suggests combining claim 89 and 96.

In response, applicants have amended claim 89 to relate to a method for imaging a fibrin-containing substance with the subject imaging agent under conditions such that the imaging agent binds to fibrin in the fibrin-containing substance, and imaging the bound imaging

agent.

Applicant respectfully states that claim 96 as a dependent claim properly recites one particular embodiment of its antecedent claim.

In view of the amendment of the claims and the preceding comments, the Examiner is respectfully requested to withdraw the rejection of claims under 35 U.S.C. §112 (second paragraph).

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the examiner to telephone him at the number provided below.

No fee, other than the enclosed $920.00 fee for a three month extension of time is deemed necessary in connection with the filing of this Amendment. However, if any other fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Gary J. Gershik 5/6/02

John P. White Date
Reg. No. 28,678
Gary J. Gershik
Reg. No. 39,9

Marked-up Version of the Amended Claims

88. (three times amended) An imaging agent which comprises a polypeptide labeled with an imageable marker, such polypeptide having an amino acid sequence which comprises at least one fifth of the amino acid sequence of the N-terminal fibrin binding domain of naturally-occurring fibronect in, [wherein the polypeptide has] and having the amino acid sequence gln-ala-gln-or met-gln-ala-gln-gln at the N-terminus of the polypeptide, and wherein the polypeptide has a molecular weight less than 31 kD [and wherein the imaging agent binds to fibrin].

89. (amended) A method for imaging a fibrin-containing substance which comprises contacting the fibrin-containing substance with the imaging agent of claim 88 under conditions such that the imaging agent binds to fibrin in the fibrin-containing substance, and imaging the bound imaging agent [detecting the presence of any imaging agent bound to fibrin and thereby imaging the fibrin-containing substance].